A no-nonsense treatment for Autism Spectrum Disorder

Editor's Choice Summary

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Overline: Neurodevelopmental disorders

Title: A no-nonsense treatment for Autism Spectrum Disorder

One-sentence summary: Mutation of the nonsense-mediated mRNA decay factor Upf2 leads to neurological phenotypes that can be corrected with immunosuppressive drugs in mice.

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Text of summary

Many genetic mutations implicated in Autism Spectrum Disorder (ASD) are in regulators of mRNA expression, processing, and translation. Among these, copy number variants of the UP-frameshift 2 (*UPF2*) gene that regulates nonsense-mediated mRNA decay (NMD) have been identified in patients with ASD. NMD is responsible for degrading mRNAs with a premature stop codon, an essential quality control mechanism limiting the creation of non-functional proteins. In Johnson et al., researchers identified new *UPF2* variants in patients with language disorder and intellectual disability, and investigated the impact of *Upf2* mutation in mouse and fly models. The results show that mice with *Upf2* deletion in excitatory forebrain neurons exhibit impairments in learning that are recapitulated in the *Upf2*-deficient fly model. *Upf2* deficient mice also showed a reduction in social interaction, as well as differences in ultrasonic vocalizations (USVs) indicative of altered communication. A transcriptomic analysis of the brains of *Upf2*-deficient mice revealed a surprising increase in genetic markers of inflammation, which was ultimately attributed to an increased number of immune cells in the brain along with elevated cytokine levels.. When the authors tested whether immunosuppressive drugs could reverse impairments in the *Upf2* deficient mice, they found that treatment with either cyclophosphamide or minocycline could correct deficits in learning, social communication, and USVs. Collectively, these results indicate that disruption of neuronal *Upf2* in mice heightens immune responses in the brain, causing behavioral changes reminiscent of ASD.

This study provides further understanding of how genetic mutations impacting mRNA and protein processing could lead to the behavioral changes associated with ASD. In the case of *UPF2* mutations, the pathological driver may be an increased activation of the brain immune system that can be targeted by immunosuppressive drugs. Now researchers can investigate whether mutations in other NMD regulators result in similar neurological impairments, and whether an immunosuppressive strategy is effective in treating patients with these mutations. A limitation of the study is the neuron-specific deletion of *Upf2* in the mouse model, which does not directly match the global expression of *UPF2* variants in patients. Nevertheless, this study exemplifies the importance of investigating expression regulators such as *Upf2* to determine how behavioral phenotypes arise, and to identify molecular changes that can be corrected by therapeutic intervention.

Highlighted Article

Johnson JL, Stoica L, Liu Y, Zhu PJ, Bhattacharya A, Buffington SA, Huq R, Eissa NT, Larsson O, Porse BT, Domingo D, Nawaz U, Carroll R, Jolly L, Scerri TS, Kim HG, Brignell A, Coleman MJ, Braden R, Kini U, Jackson V, Baxter A, Bahlo M, Scheffer IE, Amor DJ, Hildebrand MS, Bonnen PE, Beeton C, Gecz J, Morgan AT, Costa-Mattioli M.
Inhibition of **Upf2**-Dependent Nonsense-Mediated Decay Leads to Behavioral and Neurophysiological Abnormalities by Activating the Immune Response.

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